PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference MM/03061/PCT	FOR FURTHER ACTION See Form PCT/IPEA/416	
International application No. PCT/EP2004/004390	International filing date *(day/month/year)* 23.04.2004	Priority date *(day/month/year)* 15.05.2003
International Patent Classification (IPC) or national classification and IPC C07D401/12, A61K31/454, A61P29/00		
Applicant AZIENDE CHIMICHE RIUNITE ANGELINI FRANCESCO et al		

1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 7 sheets, including this cover sheet.
3. This report is also accompanied by ANNEXES, comprising:
   a. ☐ *sent to the applicant and to the International Bureau)* a total of sheets, as follows:
      ☐ sheets of the description, claims and/or drawings which have been amended and are the basis of this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).
      ☐ sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box.
   b. ☐ *(sent to the International Bureau only)* a total of (indicate type and number of electronic carrier(s)) , containing a sequence listing and/or tables related thereto, in computer readable form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).

4. This report contains indications relating to the following items:

☒	Box No. I	Basis of the opinion
☐	Box No. II	Priority
☐	Box No. III	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
☐	Box No. IV	Lack of unity of invention
☒	Box No. V	Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
☐	Box No. VI	Certain documents cited
☐	Box No. VII	Certain defects in the international application
☐	Box No. VIII	Certain observations on the international application

Date of submission of the demand	Date of completion of this report
19.11.2004	16.12.2004
Name and mailing address of the international preliminary examining authority: European Patent Office - P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk - Pays Bas Tel. +31 70 340 - 2040 Tx: 31 651 epo nl Fax: +31 70 340 - 3016	Authorized Officer De Jong, B Telephone No. +31 70 340-2833

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/EP2004/004390

Box No. I Basis of the report

1. With regard to the **language**, this report is based on the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☐ This report is based on translations from the original language into the following language , which is the language of a translation furnished for the purposes of:
   - ☐ international search (under Rules 12.3 and 23.1(b))
   - ☐ publication of the international application (under Rule 12.4)
   - ☐ international preliminary examination (under Rules 55.2 and/or 55.3)

2. With regard to the **elements*** of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report)*:

   Description, Pages

   1-23 as originally filed

   Claims, Numbers

   1-32 as originally filed

   ☐ a sequence listing and/or any related table(s) - see Supplemental Box Relating to Sequence Listing

3. ☐ The amendments have resulted in the cancellation of:
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

4. ☐ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

* *If item 4 applies, some or all of these sheets may be marked "superseded."*

Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-32
	No:	Claims	
Inventive step (IS)	Yes:	Claims	15-20
	No:	Claims	1-14,21-32
Industrial applicability (IA)	Yes:	Claims	1-32
	No:	Claims	

2. Citations and explanations (Rule 70.7):

see separate sheet

Re Item V.

The following documents are referred to in this communication:

D1 :	WO-A-98/46589	22 October 1998
D2 :	WO-A- 03/004026	16 January 2003
D3:	EP-A-908459	14 April 1999

Novelty

The compounds of formula (I) in which X is NHC(O) and the intermediates of compounds of formula (II) have not been disclosed in the prior art.

The compounds of formula (I) in which X is C(O)NHCH2 partially represent a novel selection from the compounds disclosed in D1.

The compounds of formula (I) in which X is NHC(O)CH2 partially represent a novel selection from the compounds disclosed in D2.

Therefore all the claimed subject-matter is novel.

Inventive step

1) Compounds of formula (I) in which X is C(O)NHCH2 and intermediates of formula (II)

For these compounds D1 is considered as the closest prior art. D1 discloses compounds of formula (I) (see claim 1) which are 5-HT4 receptor antagonists. This implies that these compounds can be used against pain (see e.g. D3). The compounds of D1 are not novelty destroying for claim 1 of the present application, due to the disclaimer on page 24, lines 22,23 of the present application. However the Markush formula (I) in D1 still overlaps with formula (I) in claim 1 of the present application, because R_6 (in D1) can be an aryl group substituted by **at least** a group selected from halogen and hydroxy. This means that the aryl group can e.g. be

substituted by a hydroxy group and another group.

In view of this prior art the problem was to provide further compounds which can be used as analgesic. Starting from the teaching of D1, the skilled person, faced with the problem stated above, would solve this problem by providing compounds which are covered by the definition of formula (I) in D1. He would e.g. provide compounds in which R_6 is aryl substituted by both a hydroxy group and another group (e.g. nitro, amino, nitrile).

Furthermore, the skilled person would solve the problem by providing compounds which are structurally slightly different from the compounds generically disclosed in D1. He would e.g. select compounds in which R_2 is a propyl group instead of an isopropyl group.

The skilled person would thus come to the compounds of the present application without an inventive step.

The intermediates of formula (II) are not inventive either because they do not benefit from the inventivity of the end products. Also it is noted that claim 30, which is directed to these intermediates, does not contain the proviso as in claim 1 (page 24, lines 23,24). This means that a part of the compounds claimed in claim 30 are not intermediates for the end products.

2) Compounds of formula (I) in which X is NHC(O)CH2

For these compounds D2 is considered as the closest prior art. D2 discloses compounds of formula I (see claim 1) which are analgesics. The Markush formula I in D2 overlaps with formula (I) in claim 1 of the present application, in case (in D2) R^2, R^3, R^4 are hydrogen and R^1 is an optionally substituted heteroaryl group. In this respect it is noted that the possibility of having condensed heterocyclic rings in this position is specifically mentioned in D2 on page 6. An indazole ring is however not specifically mentioned.

In view of this prior art the problem was to provide further compounds which can be used as analgesic. Starting from the teaching of D2, the skilled person, faced with the problem stated above, would solve this problem by providing compounds which are covered by the definition of formula (I) in D2. He would e.g. provide compounds according to claim 1 of D2 in which R^1 is an optionally substituted indazol-2-yl group and in which R^2, R^3, R^4 are hydrogen. The skilled person would thus come to the compounds of the present application without an inventive step.

(It is noted that the present application does not provide examples of compounds in which X is NHC(O)CH2)

3) Compounds of formula (I) in which X is NHC(O)

For these compounds D1 is considered as the closest prior art. These compounds are considered as inventive.

Remarks concerning the applicants letter of 18.11.2004

According to the applicants letter, the compounds of the present application can be used against chronic pain, while in the prior art documents do not refer to **chronic** pain. However it is commonly known in the art, that conventional drugs (e.g. serotoninergic agents) can be used against chronic pain. In any case there is no reason for the skilled person to believe that the compounds of D1 and D2 would only be effective in treating acute pain. Furthermore it is noted that the tests carried out in the present application only show the activity of the compounds against acute pain in rats.

According to the applicant, rearranging the compounds of the invention in different groups for assessing inventive step is inadmissible. However it is clear that in case of a Markush formula, it is in principle possible that different compounds falling within the Markush formula have a different closest prior art. This is of course also a sign that the application does not relate to a single invention, contrary to what is required by Rule 13 PCT. It is however our policy to make "non unity" only in cases which are very clear.

According to the applicant there is a third group of compounds where X is NHC(O), which has been inexplicably disregarded. This statement is incorrect as this third group of compounds has been discussed in our previous communication.

Document D3 is analysed in very much detail by the applicant and the applicant comes to the conclusion that D3 is of no help in assessing inventive step of the present invention. However it is clear from our objection (in which D3 is mentioned casually), that D3 is only cited to show that 5-HT4 receptor antagonists can be used in the treatment of pain. Anyway it is common knowledge in the art that chronic pain can be treated by compounds with 5-HT4 activity.

In the discussion of compounds of group II, the applicant states that our argumentation fails to explain why the document D2 would have prompted the skilled person to modify the compounds of D2. However it is not necessary for the skilled person to modify the compounds of formula (I) disclosed in D2, since the compounds of the present application are covered by the generic teaching disclosed in D2. The skilled person would, in order to solve the problem, simply choose one of the compounds according to formula (I) in D2 and would thus come to compounds of the present application.